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Early Liver Transplantation for Severe Alcoholic Hepatitis

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1. Introduction

Although alcohol-associated liver disease (ALD) has long been a major component of the liver disease landscape, it was overshadowed by chronic hepatitis C (HCV) until recently. Nevertheless, with the declining incidence of HCV in the wake of highly effective antiviral therapy, attention has shifted to the increasing burden of ALD in the United States (US). The incidence of advanced ALD, including acute alcoholic hepatitis (AH) and alcohol-associated cirrhosis, is rising the US, with the largest increase in mortality due to ALD among young people and women.(1, 2) Unsurprisingly, rates of alcohol use, including binge drinking and alcohol use disorders (AUD), have likewise surged over the past 10 years, rising 80% in women alone with consequent increases in mortality in much of the US.(3, 4) As a result, ALD is now the most common indication for liver transplantation (LT) in the US, with LT rates for acute AH rising as well.(5) The publication of the first pilot trial of LT for AH in 2011 showed that outcomes were favorable for highly selected patients with AH and recent

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drinking.(6) Following this, LT for AH became more common, in spite of the sparse guidance regarding candidate selection, counseling, post-operative care, long-term follow up, and other best practices.

2. Current state of the evidence: What are the outcomes?

Historically, mortality rates for severe AH unresponsive to standard medical therapy were abysmal, with six-month mortality rates upwards of 70%(7) and one-year mortality rates in excess of 90%.(8) For these reasons, several recent studies have challenged the traditional six-month abstinence rule, investigating the efficacy of LT in select patients with severe AH unresponsive to standard medical therapy.(6)(9)(10)(11) Nearly a decade ago, Mathurin *et al.*(6) were the first to show the survival benefit of early LT prior to six months of abstinence in highly selected candidates with severe AH unresponsive to corticosteroids as their initial decompensating event. Candidates went through a rigorous assessment process including evaluation by multiple teams prior to addition to the waiting list and an exhaustive assessment completed by a trained addiction specialist. Importantly, nearly 90% of candidates were deemed not suitable for LT, largely due to concerns raised during their psychosocial evaluation. The 26 candidates who underwent early LT had significantly greater six-month survival rates when compared to those who did not receive a LT (77 vs. 23%, $p<0.001$), without significant relapse.

The benefit of early LT for severe AH was confirmed by subsequent studies in the US.(9)(10) Im *et al.*(9) published their single-center experience from Mount Sinai Medical Center in New York in which six-month survival again favored early LT in those not responding to several medical therapies that included both corticosteroids, pentoxifylline and/or *N*-acetylcysteine (89 vs. 11%, $p<0.001$). Importantly, over 90% of candidates were again excluded due to concerning psychosocial profiles with only 9/94 candidates evaluated undergoing LT. One recipient had alcohol relapse but was still alive at the time the study was published at day 660. Lee *et al.* (10) published a subsequent single-center pilot study at Johns Hopkins University in which 17 subjects admitted to the hospital with severe AH unresponsive to standard medical therapy as their initial decompensating event underwent early LT. When compared to the 36 subjects with alcohol-related cirrhosis and at least six months of sobriety, six-month survival was similar (100 vs. 89%, $p=0.27$) as were rates of relapse (24 vs. 29%, $p>0.99$). Nevertheless, the authors observed increased high-risk drinking patterns defined as binge (>6 units of alcohol in one day for males or >4 units for females) or frequent drinking (alcohol use in ≥4 consecutive days). Similar to previous studies, 93% were declined for transplantation listing.

Efforts to expand these single-center findings were undertaken by the multicenter American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH).(11) This retrospective US-based 12-center study enrolled 147 early LT recipients between 2006-2017 with a first episode of hepatic decompensation due to ALD without a prior diagnosis of ALD. Candidates were required to have strong social support as determined by a transplant social worker with detailed substance abuse evaluation and were expected to adhere to lifelong alcohol abstinence. Eleven of the 12 centers had additional evaluation by an addiction specialist. In this highly selected, standardized patient population, one and three

year survival rates (94 and 84% respectively) were not only similar to previous single center studies, but approximated published rates for all LT recipients. Rates of relapse with sustained alcohol use were low at 10% and 17% at one and three years after LT.

Given these findings, the July 2019 Diagnosis and Treatment of Alcohol-Related Liver Diseases guidelines from the American Association for the Study of Liver Diseases (AASLD)(12) recommend consideration of early LT in carefully selected patients with favorable psychosocial profiles with severe AH not responding to medical therapy, but cautions that there are several issues requiring further study before this practice is widely adapted, including how to best standardize recipient selection in order to maximize post-LT survival and minimize relapse. The AASLD also cautions that substantial questions remain regarding the optimal use and timing of AUD treatment following LT in addition to the potentially negative public perception of allocating the limited supply of donor organs to recipients with active AUD, an awareness that may adversely impact organ donation rates. The AASLD suggests that future research is needed to clarify these issues through the conduct of prospective studies that investigate the utility of early LT with severe AH, focusing on patient selection, monitoring of alcohol use, and treatment of AUD before and after LT.

Following the recent AASLD guideline update, Lee *et al.*(13) developed a mathematical model simulating early versus delayed LT for severe AH that incorporated post-LT drinking patterns, including abstinence, a slip (brief alcohol use followed by sobriety) or sustained use. Based on their model, the authors found that patients offered early LT had an estimated average life expectancy of 6.6 years compared with 1.5 years for patients offered delayed LT (4.5-fold increase). The greatest benefit was derived by offering early LT for severe AH, where predicted survival increased to 10.9 years if there was no relapse. A benefit was still seen with early LT even if the recipient had sustained alcohol use after LT, with a predicted survival of 3.6 years, indicating that early LT is superior to delayed LT for patients with severe AH independent of alcohol relapse.

3. Defining and diagnosing alcoholic hepatitis

AH patients may exist anywhere on the spectrum ranging from asymptomatic to florid liver failure. As AH is largely a clinical syndrome with corresponding histopathology of steatohepatitis due to ALD (ASH), liver biopsy is not always required to diagnose AH.(12, 14, 15) In fact, many asymptomatic patients will have elements of ASH on biopsy that may include degenerative changes in hepatocytes (e.g., ballooning or Mallory-Denk inclusions), neutrophilic lobular inflammation, pericellular fibrosis and/or steatosis.(16) Underlying cirrhosis due to ALD can be present in upwards of 40% of patients with AH.(17) As ~% of patients with AUD and abnormal liver associated enzymes have an additional chronic liver disease,(18) the 2018 Clinical Practice Guidelines: Management of Alcohol-Related Liver Disease from the European Association for the Study of the Liver (EASL) recommend liver biopsy for phase II and phase III research trials and clinically if there are either inconclusive non-invasive test results or suspicion for competing liver disease, but cautions that biopsy should not be used in every patient with AH, emphasizing that the risks of biopsy should carefully be weighed against the benefits and therapeutic consequences.(15) To standardize

both clinical and research approaches, the National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Alcoholic Hepatitis Consortia in 2016 established standard criteria for the diagnosis of AH,(14) which can be defined as definite, probable, or possible (Table 1). The AASLD recommends that these standard diagnostic criteria be applied to any patient in whom AH is suspected.

4. Determining prognosis: Who will and will not require liver transplantation?

Distinguishing which patients with AH will require LT is of utmost importance given both the continued organ shortage and the desire to avoid unnecessary LT in a patient who may recover from their AH with abstinence, nutritional support, and medical therapy. Several laboratory-based prognostic scores exist to aid transplant providers in making this vital decision including Age, serum Bilirubin, INR and serum Creatinine (ABIC) score, the Glasgow Alcoholic Hepatitis Score (GAHS), the Lille model, the Maddrey Discriminant Function (MDF), the Model for End Stage Liver Disease (MELD) score, and the MELD-Lille score (Table 2).(12, 19) Each score can be calculated based on readily-available laboratory information, much of which is shared across the different clinical decision aids. While each score has advantages and disadvantages, including the lack of specificity to avoid unnecessary LT, MDF or MELD score for diagnosis of severe AH and the Lille model for determining response to medical treatment after seven days are the most widely endorsed by multiple clinical practice guidelines.(12, 15, 20)

The MDF was developed in 1978 in a *post-hoc* analysis of an early AH clinical trial investigating the benefit of corticosteroids compared with placebo.(21) Maddrey *et al.* (21) found that when using serum bilirubin and INR, a MDF score ≥32 identified which of their 55 trial participants had severe AH and were at high risk for 28-day mortality. Over the next several decades, the MDF has been incorporated into most AH clinical trials, having withstood the test of time in guiding clinical decisions vis-à-vis in whom to initiate corticosteroid therapy. Nonetheless, MDF is limited in predicting both intermediate and long-term outcomes as well as corticosteroid treatment response. In order to further optimize selection of patients appropriate for corticosteroid therapy given the risk profile of this treatment, Forrest *et al.*(22) developed the GAHS from a cohort of 225 subjects with AH. The GAHS, calculated using age, blood urea nitrogen, INR, serum bilirubin, and white blood cell count, ranges from 5-12 with a score ≥ 9 associated with a poor prognosis. Furthermore, the authors found that in their subgroup of 144 subjects with severe AH defined by MDF ≥32 and a GAHS ≥9, there was both a 28- (78 *vs.* 52%, p=0.002) and 84-day survival benefit for corticosteroid treatment (59 *vs.* 38%, p=0.020). Nevertheless, the GAHS has yet to be validated outside of the United Kingdom, limiting its generalization. The MELD score has also been applied to AH prognosis(23) and more recently, has been suggested as a way to determine need for corticosteroid initiation.(12, 24) In their seminal paper, Dunn *et al.*(23) performed a retrospective cohort analysis of 73 subjects with AH, reporting that MELD was comparable to MDF in predicting short- and intermediate mortality at 30- and 90-days respectively.

Developed by Dominguez *et al.*,(25) the ABIC score, which incorporates age plus three variables common to the MELD score, serum bilirubin, INR and creatinine, was developed from a derivation cohort of 103 subjects with biopsy-proven AH and validated in a separate 80 subject confirmatory cohort. The addition of age to the baseline calculation improved prediction of short, intermediate and long-term mortality at 3, 6, and 12-months, respectively, when compared to GAHS, MDF, and MELD score. When the ABIC score was calculated with day seven laboratories and compared with the Lille model, the ABIC score had greater predictive accuracy for determining 6-month mortality (AUROC 0.84 *vs.* 0.62, $p<0.001$). Yet, this was not validated by future study where the performance of ABIC was similar to MDF and GAHS but was less accurate at predicting 3-month mortality than MELD.(26) Moreover, the ABIC score has yet to be validated outside of Spain and for these reasons, is not endorsed by any societal guidelines at this time.

The Lille model has an inherent advantage over other clinical decision aids in that it is the only dynamic assessment.(7) The Lille model combines age, albumin, renal function, prothrombin time, serum bilirubin, and change in serum bilirubin at day seven. In their landmark study, Louvet *et al.*(7) found that the Lille model outperformed all other clinical decision aids in predicting six-month mortality in both their derivation (AUROC 0.89) and validation cohorts (AUORC 0.85). The authors also determined that since a cutoff of > 0.45 predicted poor prognosis and lack of response to corticosteroid treatment, this finding should prompt the clinician to discontinue this treatment and consider early LT. Non-responders had a 25% 6-month mortality compared with 85% for responders, $p<0.001$. Importantly, 40% of their population had a score of >0.45. A recent study suggests that calculation of the Lille model at day four of treatment rather than day seven is just as accurate and may facilitate even timelier referral for early LT, although this has yet to be widely adapted into practice, requiring further validation.(27) Also, Louvet *et al.*(24) examined the combination of the dynamic Lille model with multiple static models. They found that the addition of MELD score to the Lille model better predicted outcomes in AH using multinational data from 604 subjects and was more accurate than Lille + MDF or Lille + ABIC. Furthermore, for subjects with MELD ≥ 21 and Lille ≥ 0.45, there was a 1.9-fold increased risk of death compared with complete responders (Lille 0.16) with similar MELD. The authors suggest that Lille + MELD score should be incorporated into both clinical decision making and AH clinical trials.

5. Transplant candidate selection

Despite the abundance of data detailed above, transplant for AH has been occurring largely without using consensus criteria, prompting a national expert consensus meeting in Dallas, Texas in April 2019, which culminated in the publication of guidance for centers contemplating or already performing AH transplant,(28) on which selection criteria for AH transplant were proposed. Overall, selection is grounded on three ethical principles: urgency, utility, and equity. Urgency demands that the sickest get transplanted first, best illustrated by the use of the MELD score in allocation. Though AH patients easily meet urgency criteria given how often their MELD scores are markedly elevated, they also have urgent psychosocial issues that must be addressed and treated. Utility requires achievement of the greatest good for the greatest number that evaluates post-LT outcomes in addition to other

factors. The best example of its application to LT is the use of the Milan criteria, which seek to exclude those who might have greater cancer recurrence post-transplant. Post-transplant alcohol relapse risk and its assessment ensures that patients with acceptable risk of relapse are chosen, particularly as post-transplant alcohol use, particularly substantial alcohol use, does lead to graft loss and earlier mortality.(29) In a larger, retrospective study of AH transplant in the US, relapse to heavy alcohol use was 10% at one year and 17% at three years follow-up.(11) While there are several alcohol relapse risk assessments that were recently reviewed(30), including the novel but unvalidated Sustained Alcohol use post Liver Transplant (SALT) score for AH LT, a single recommended structured relapse risk assessment does not exist.(31) Equity is the requirement that allocation and selection proceed fairly, with AH patients afforded equal opportunities for LT as do other patients with behaviors that may have contributed to their liver disease, such as obese patients with nonalcoholic steatohepatitis, or former intravenous drug users with HCV. Deprioritizing patients solely because of addiction to alcohol or other appeals to perceived social worth were deemed unethical and should not be used as selection criteria.

The Dallas consortium selection criteria emphasized two broad domains: medical and psychosocial selection. Medical selection criteria include an accurate diagnosis of AH according to the NIAAA clinical trial definitions as detailed in Table 1 (32), failure of or contraindication to medical therapy (prednisolone), use of MELD and Lille scores to establish prognosis, absence of medical contraindications to LT, and first presentation of decompensated liver disease. Psychosocial criteria were more numerous and include absence of uncontrolled psychiatric disease, absence of comorbid untreated substance use (excluding marijuana), an acceptable relapse risk profile as assessed by qualified addiction medicine specialists, no more than one failed attempt at maximal alcohol rehabilitation (typically inpatient alcohol treatment or intensive outpatient programs), acceptable insight of the patient and their social supports regarding alcohol use disorder and need for treatment, at least two supportive family members or friends, and commitment to lifelong sobriety and alcoholism treatment. The elements of the psychosocial evaluation are broad; they include an assessment of other known risks for relapse, including a thorough alcohol, substance use, and mental health history, history of current and former alcohol and substance use treatment and outcomes, treatment adherence history, and sober social support.

Notably, a defined abstinence timeframe was not recommended. The so-called “six-month rule,” which excluded patients with less than six-months of alcohol abstinence from consideration for LT had been promulgated and used widely in selection for patients with ALD undergoing LT evaluation. Nevertheless, more recent data confirmed that the six-month cutoff was not supported as a reliable indicator of post-transplant relapse risk. In a seminal prospective study of post-transplant ALD patients, DiMartini *et al.*(33) confirmed that while longer abstinence was associated with superior outcomes, there was no specific cutoff at six-months that could be used to predict relapse risk. Furthermore, a growing body of data from centers performing AH transplant has shown favorable one and three year survival and relapse risk outcomes, despite candidates having substantially < 6 months’ alcohol abstinence.(11)

6. Center-specific criteria for AH transplant

The Dallas Consortium strongly recommended certain center-specific program requirements as well. The biggest change is in the broader recognition of the crucial importance of integrated addiction specialists within the transplant team and the need for transplant centers to take full responsibility for management of *both* ALD and AUDs. Since AH patients are amongst the most medically and psychosocially complex patients commonly encountered, any consideration for transplanting such patients requires a well-functioning, highly relational transplant team with a well-integrated addiction specialist, in addition to existing social work evaluation requirements in order to provide necessary expert guidance on the array of complex psychosocial issues that arise in AH patients. Transplant programs considering AH transplant should be required to have a qualified addiction-trained staff member, whether social worker, psychologist, psychiatrist, or addiction medicine trained physician. Robust post-transplant relapse assessment, in the form of regular in-person questioning, structured alcohol use questionnaires, and use of alcohol use biomarkers is necessary, as is a process to identify relapse early in order to facilitate the swift referral of patients suffering from slips or relapses with alcohol use treatment, whether at the transplant center or locally. Transparency in selection along with structured program-level data collection was recommended as well. A consensus of the entire transplant team developed during regular meetings is recommended before proceeding to transplant.

7. Conclusions

The changing landscape of liver transplant in the US and the rise of ALD and acute AH as transplant indications mandates more structured selection criteria. The Dallas Consortium AH Transplant criteria represent a welcome step forward in ensuring that more AH patients are appropriately considered for transplant and that this process proceeds in a scientifically rigorous, transparent, and ethical manner.

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Abbreviations:

ABIC	Age, serum Bilirubin, INR and serum Creatinine
AH	Acute alcoholic hepatitis
AASLD	American Association for the Study of Liver Diseases
ALD	Alcohol-related liver disease
ASH	Steatohepatitis due to ALD
AUD	Alcohol use disorder
EASL	European Association for the Study of the Liver

GAHS	Glasgow alcoholic hepatitis score
HCV	hepatitis C
LT	Liver transplantation
MDF	Maddrey Discriminant Function
MELD	Model for end stage liver disease
NAC	N-acetyl cysteine
NIAAA	National Institute on Alcohol Abuse and Alcoholism

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Table 1.

Diagnosis of Alcoholic Hepatitis [Adapted from (12, 14)]

Definite	**Probable**	**Possible**
Clinical features: • AST >50, AST/ALT >1.5, and both values < 400IU/L • Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice • Onset of jaundice within the prior 8 weeks • Total bilirubin >3.0 mg/dL **Biopsy features:** • Hallmarks include neutrophilic lobular inflammation, degenerative changes in hepatocytes (ballooning and Mallory-Denk inclusions), steatosis, and pericellular fibrosis • Underlying cirrhosis present in 30-40% of patients	**Clinically diagnosed without the presence of the following confounding factors**: • Atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80 • Possible drug-induced liver disease (suspect drug taken within 30 days of onset of jaundice) • Possible ischemic hepatitis (e.g., severe upper gastrointestinal hemorrhage, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha-1 antitrypsin deficiency) • Uncertainties about alcohol use assessment (e.g., patient denies excessive alcohol use)	**Clinically diagnosed with one or more of the following confounding factors present**: • Atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80 • Possible drug-induced liver disease (suspect drug taken within 30 days of onset of jaundice) • Possible ischemic hepatitis (e.g., severe upper gastrointestinal hemorrhage, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha-1 antitrypsin deficiency) • Uncertainties about alcohol use assessment (e.g., patient denies excessive alcohol use)

ALT=alanine aminotransferase; ANA=anti-nuclear antibody; AST=aspartate aminotransferase; SMA=smooth muscle antibody

Table 2.

Clinical Decision Aids Based on Clinical Data Used for Alcoholic Hepatitis Prognostication

Test	Description	Cutoffs	Clinical Use	Advantages	Disadvantages	Guideline Recommended
ABIC score	Age, serum bilirubin, INR, creatinine	Low risk for mortality <6.71 Intermediate risk 6.71-9.0 High risk >9.0	Prognosis	3 risk categories Possible dynamic use at Day 7 for prognostication	Threshold for corticosteroid initiation remains uncertain Only verified in Spain	None
GAHS	Age, BUN, PT/INR, serum bilirubin, WBC	Severe AH ≥9	Initiation of corticosteroids if MDF ≥32 and GAHS ≥9	Improves performance of MDF when severe AH diagnosed (MDF >32)	Only verified in United Kingdom	EASL
Lille model	Age, albumin, serum bilirubin (day 0 and day 7), creatinine, PT	Corticosteroid response <0.45 Nonresponse ≥0.45 (partial response 0.46-0.56)	Response to corticosteroids	3 risk categories Dynamic assessment Early discontinuation of corticosteroids in non-responders.	Partial response creates uncertain clinical decision making	AASLD, ACG, EASL
MDF	INR, serum bilirubin	Severe AH ≥32	Disease severity and initiation of corticosteroids	Decades of use for AH Used by most AH trials	False positives may lead to unnecessary corticosteroid treatment Inferior prediction of mortality beyond 30-days	AASLD, ACG, EASL
MELD score	Creatinine, INR, serum bilirubin, sodium	Severe AH ≥21	Disease severity and prognosis	Decades of use for hepatology and LT	Threshold for corticosteroid initiation remains uncertain	AASLD, ACG

AASLD=American Association for the Study of Liver Diseases; ABIC=Age, serum Bilirubin, INR and Creatinine; ACG=American College of Gastroenterology; AH=alcoholic hepatitis; AUROC=area under the receiver operator curve; BUN=blood urea nitrogen; EASL=European Association for the Study of the Liver; GAHS=Glasgow Alcoholic Hepatitis Score; LT=liver transplant; MDF=Maddrey discriminant function; MELD=Model for end stage liver disease; PT=prothrombin time; WBC=white blood cell